Step Therapy Is Not Appropriate for Antiepileptic Drugs

To the Editor:

We read with interest the article by Payakachat and colleagues, comparing the clinical practice guidelines for treatment of new-onset epilepsy in adults.[1] While we appreciate their efforts to provide a careful review of available treatment guidelines and consideration of how these guidelines might be applied in managed care, we strongly disagree with their conclusion that older agents (i.e., phenobarbital, carbamazepine, phenytoin, and valproate) are the preferred first-line treatments for new-onset epilepsy. Their conclusions appear to be based upon a rather narrow consideration that only accounts for efficacy in controlling seizures. As the authors correctly note, broader data on the effectiveness, outcomes, tolerability, and quality of life are lacking in the published literature. However, the authors underemphasize important aspects of epilepsy as a disorder and characteristics of antiepileptic drugs that must be a part of therapeutic and formulary decision making. Indeed, the guidelines that are included in the article make specific statements about drug selection in epilepsy contrary to the conclusion of Payakachat et.al. The following are important factors, essential to therapeutic decisions in new-onset epilepsy, that had they been included would probably have led to a different conclusion.

Epilepsy is a heterogeneous disorder. Seizures are often merely the primary clinical manifestation of an underlying neurological abnormality or disease. Although seizures may appear to be similar in clinical presentation or electrographically, the underlying pathology can be very different from one patient to the next. Until better diagnostic tools are available to determine the underlying pathophysiology of seizures, it is important to have a broad group of drugs with respect to mechanisms of action and adverse events from which selections can be made.

The published guidelines clearly demonstrate that drugs need to be matched to the seizure type and/or seizure syndrome. Without careful attention to this detail, incorrect antiepileptic drugs may be selected and could result in exacerbation of seizures rather seizures and primary generalized seizures. Initiation of carbamazepine or phenytoin in a patient with certain types of primary generalized seizures will often result in increased seizure frequency.[2-4] In all of the guidelines, some of the seizure syndromes only have a single older and newer drug recommended as first-line therapy. Typically, the older agent is valproate, which is associated with numerous adverse effects and teratogenicity.

This evaluation and recommendation does not account for the numerous adverse effects associated with older antiepileptic drugs. Older agents are associated with side effects that often result in discontinuation, impairment of lifestyle, or, in rare cases, life-threatening conditions. In several clinical trials, the newer antiepileptic drugs have demonstrated greater tolerability compared with the older agents.[5-8] Beyond these acute adverse effects, chronic adverse effects such as osteopenia and osteoporosis are clearly associated with the older antiepileptic drugs.[9,10] Recent studies have also provided increased understanding of the teratogenicity of the older agents, especially phenobarbital and valproate, making them less than optimal options for women of child-bearing potential.[11-14]

The newer agents are clearly associated with fewer drug interactions.[15] All of the older drugs are hepatically metabolized, are potent inducers or inhibitors of hepatic enzymes, and some are highly protein bound. Not only do these features make them prone to influences by other medications, but their effects on hepatic enzymes will change the efficacy of other drugs the patient may be taking. One example is the clear interaction between many of the older agents and hormonal contraceptives, rendering the hormonal contraceptive much less effective.[16-19] Newer antiepileptic drugs often involve renal elimination, do not induce or inhibit hepatic enzymes to the extent of the older drugs, and are typically free of drug interactions. This is a key factor when selecting an antiepileptic drug in patients who are taking multiple medications.

We believe that a recommendation for antiepileptic drug selection must take into account all of these factors to form a comprehensive evidence-based approach. Restrictions on new antiepileptic drug use in a stepped formulary approach fails to recognize the highly heterogeneous nature of epilepsy and forces patients to be exposed to drugs that are not well tolerated, carry greater risk for chronic adverse effects and teratogenicity, and complicate the therapeutic regimen with multiple drug interactions. A more thorough analysis of all available data should be initiated prior to making formulary decisions regarding antiepileptic drug use for epilepsy in managed care.

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DISCLOSURES

Dr. Welty serves as a consultant for MedPointe Pharmaceuticals and Ovation Pharmaceuticals. Dr. Faught and Dr. Privitera serve as consultants for and receive grants from all pharmaceutical manufacturers of antiepileptic drugs.

REFERENCES

1. Payakachat N, Summers KH, Barbuto JP. A comparison of clinical practice guidelines in the initial pharmacological management of new-onset epilepsy in adults. *J Manag Care Pharm*. 2006;12(1):55-60.

2. Gelisse P, Genton P, Kuate C, Pesenti A, Baldy-Moulinier M, Crespel A. Worsening of seizures by oxcarbazepine in juvenile idiopathic generalized epilepsies. *Epilepsia*. 2004;45(10):1282-86.

3. Genton P, Gelisse P, Thomas P, Dravet C. Do carbamazepine and phenytoin aggravate juvenile myoclonic epilepsy? *Neurology*. 2000;55(8):1106-09.

4. Horn CS, Ater SB, Hurst DL. Carbamazepine-exacerbated epilepsy in children and adolescents. *Pediatr Neurol*. 1986;2(6):340-45.

5. Privitera MD, Brodie MJ, Mattson RH, Chadwick DW, Neto W, Wang S. Topiramate, carbamazepine and valproate monotherapy: double-blind comparison in newly diagnosed epilepsy. *Acta Neurol Scand*. 2003;107(3):165-75.

6. Brodie MJ, Chadwick DW, Anhut H, et al. Gabapentin versus lamotrigine monotherapy: a double-blind comparison in newly diagnosed epilepsy. *Epilepsia*. 2002;43(9):993-1000.

7. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res*. 1999;37(1):81-87.

8. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet*. 1995;345(8948):476-79.

9. Boluk A, Guzelipek M, Savli H, Temel I, Ozisik HI, Kaygusuz A. The effect of valproate on bone mineral density in adult epileptic patients. *Pharmacol Res*. 2004;50(1):93-97.

10. Kulak CA, Borba VZ, Bilezikian JP, Silvado CE, Paola L, Boguszewski CL. Bone mineral density and serum levels of 25 OH vitamin D in chronic users of antiepileptic drugs. Arq *Neuropsiquiatr*. 2004;62(4):940-48.

11. Vajda FJ, O'Brien T J, Hitchcock A, et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *J Clin Neurosci*. 2004;11(8):854-58.

12. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. *Acta Paediatr*.2004;93(2): 174-76.

13. Artama M, Auvinen A, Raudaskoski T, Isojarvi I, Isojarvi J. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology*. 2005;64(11):1874-78.

14. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) pregnancy registry: a 6-year experience. *Arch Neurol*. 2004;61(5):673-78.

15. Patsalos PN, Froscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. *Epilepsia*. 2002;43(4):365-85.

16. Crawford P. Best practice guidelines for the management of women with epilepsy. *Epilepsia*. 2005;46(suppl 9):117-24.

17. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. *Br J Clin Pharmacol*. 1990;30(6):892-96.

18. Huang SH, Gambi F, Conti F, et al. Antiepileptic drugs lower contraceptive sex hormone and increase the risk of unplanned pregnancies in women with epilepsy: revisited study. *Int J Immunopathol Pharmacol*. 2003;16(2):181-83.

19. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br *J Clin Pharmacol*. 2006;61(3):246-55.

The Authors Respond

Comparison of Clinical Practice Guidelines in the Initial Pharmacological Management of New-Onset Epilepsy in Adults

We appreciate the consideration given to our article by Welty, Fraught, and Privitera; however, we disagree. The authors make a vague statement, "the guidelines that are included in the article make specific statements about drug selection in epilepsy contrary to the conclusion of Payakachat"; however, after making this statement they proceed to cite several primary research articles and do not actually support this claim from the text of the guidelines.

Their title "Step therapy is not appropriate for antiepileptic drugs" is misleading because our article was an examination and comparison of guidelines. The guidelines do not advocate step therapy nor were we acting as advocates of step therapy. Our intent was to compare guideline recommendations. This is not tantamount to advocating step therapy. Rather, we observed that published guidelines did not clearly delineate supremacy of the newer drugs over the older drugs.

Guidelines are intended as general guides. They do not preclude deviation when specific circumstances warrant it. The authors note exceptions or special circumstances that they advocate as advantageous for the newer drugs. However, it is notable that the authors of the guidelines did not find these issues sufficiently convincing to discount the use of older drugs in all cases.

The authors introduce some subjects that are "non sequiturs" for our article. The authors state, "Epilepsy is a heterogeneous disorder. Seizures are often merely the primary clinical manifestation of an underlying neurological abnormality or disease." However, our article is not about epilepsy as a disease nor about seizures as a manifestation of varied diseases. The authors go on to say, "Although seizures may appear to be similar in clinical presentation or electrographically, the underlying pathology can be very different from one patient to the next." Our article was also not about the specific pathology underlying seizures. The authors continue, "Until better diagnostic tools are available to determine the underlying pathophysiology of seizures, it is important to have a broad group of drugs with respect to mechanisms of action and adverse events from which selections can be made." Again, our article was not about seizure diagnosis, nor underlying pathophysiology, nor the importance of having treatment options. Rather, our article compared the conclusions reached in published treatment guidelines.

Also notable is the observation that the guidelines do not make a strong case for the use of newer drugs over the older drugs. This is not the same as precluding use of the newer drugs. Rather, in the era of cost-conscious health care, we only observed that the guidelines do not make a strong case for the newer drugs in the initial management of newly diagnosed epilepsy. And, the newer drugs are more expensive—thus